

Application No. 10/069,018

Supplemental Amendment dated December 19, 2003

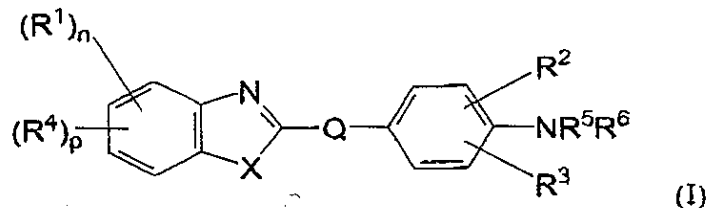
Page 2

Amendments to the Claims:

The following claims will replace all prior versions of the claims in this application (in the unlikely event that no claims follow herein, the previously pending claims will remain):

1-25. (Cancelled).

26. (Previously presented) An arylbenzazole compound represented by the structural formula I below, or a pharmaceutically acceptable salt thereof,



wherein

X represents S or O;

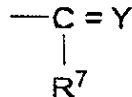
R¹ independently represents fluoro, iodo or trimethyltin;

R² represents hydrogen, NO₂, N₃, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF₃;

R³ represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

R⁴ independently represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R⁵ and R⁶ each independently represent hydrogen, an amino acid, an alkyl, or a group



wherein Y represents O or S, and R⁷ represents alkyl or -CH(R⁸)NH₂ where R⁸ represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, -CH₂- or -CH=CH-;

p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

Application No. 10/069,018

Amendment dated December 19, 2003

Page 3

subject to the following provisos:

- (a) alkyl or substituted alkyl groups include linear, branched or cyclic structures but when present as linear or branched structures in the compound or as a moiety in another group such as alkoxy they are composed of less than ten carbon atoms;
- (b) p represents zero or 1 when n represents 3;
- (c) when n represents zero, at least one of R⁵ or R⁶ represents -C(Y)-CH(R⁸)NH₂;
- (d) when a group is optionally substituted, unless otherwise specified, the substituent is selected from one or more of the following: a halogen, OH, SH, NH₂, COOH and CONH₂.

2 27. (Previously presented) An arylbenzazole compound of claim 26 with at least one of the following features:

- (a) alkyl groups when present as such or as a moiety in other groups such as alkoxy each contain less than six carbon atoms;
- (b) at least some alkyl groups when present as such or as a moiety in ether groups such as alkoxy are methyl or ethyl; or
- (c) halogen substituents, when present, are selected from fluorine, iodine, bromine and chlorine.

3 28. (Previously presented) An arylbenzazole compound of Claim 27 where the halogen substituent is fluorine.

4 29. (Currently amended) An arylbenzazole compound of Claim 29 28 wherein the ~~compound incorporates the~~ said fluorine substituent is the isotope ¹⁸F.

5 30. (Previously presented) An arylbenzazole compound of Claim 26 or 27 wherein R¹ is fluorine.

6 31. (Previously presented) An arylbenzazole compound of claim 26 wherein R¹ is in the 5-position of the benzazole moiety.

Application No. 10/069,018
Amendment dated December 19, 2003
Page 4

- 7 32. (Previously presented) An arylbenzazole compound of claim 26 wherein R^2 is a substituent in the 3' position of the phenyl group.
- 8 33. (Previously presented) An arylbenzazole compound of claim 26 wherein X is sulphur.
- 9 34. (Previously presented) An arylbenzazole compound of claim 26 wherein one of R^1 and R^2 is $C(Y)-CH(R^3)NH_2$ or a salt thereof, and the other is hydrogen.
- 10 35. (Previously presented) An arylbenzazole compound of claim 26 wherein Y is O and R^3 is selected from hydrogen, $-CH_3$, $-(CH_2)_4NH_2$ or $-CH_2OH$.
36. (Cancelled)
37. (Cancelled)
38. (Cancelled)
- 11 39. (Previously presented) An arylbenzazole compound which is one of the following:
4 Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
6 Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
4 Fluoro-2-(4'-aminophenyl)benzothiazole;
6-Fluoro-2-(4'-aminophenyl)benzothiazole;
4,5-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
4,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
5,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
7-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
6,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

Application No. 10/069,018

Amendment dated December 19, 2003

Page 5

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;
5-Fluoro-2-(4'-aminophenyl)benzothiazole;
4-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;
5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;
6-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;
4-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;
5-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;
6-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;
4-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;
5-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;
6-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;
2-(4'-Aminophenyl)benzothiazole alanyl amide hydrochloride salt;
2-(4'-Amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;
2-(4'-Amino-3'-chlorophenyl)benzothiazole alanyl amide hydrochloride salt;
2-(4'-Aminophenyl)benzothiazole lysyl amide dihydrochloride salt;
2-(4'-Amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;
2-(4'-Amino-3'-chlorophenyl)benzothiazole lysyl amide dihydrochloride salt;
2-(4'-Amino-3'-methylphenyl)benzothiazole serine hydrochloride salt;
6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;
5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;
6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;
5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;
5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt;
5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;
7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;
5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole;
5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;
4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;
6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

Application No. 10/069,018

Amendment dated December 19, 2003

Page 6

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole;
5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;
5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt; and
5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole.

12
40. (Previously presented) An arylbenzazole compound of claim 26 for use in therapy as an active therapeutic substance wherein said arylbenzazole compound is an acid addition salt derived from an acid selected from the group consisting of: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzenesulphonic, methanesulphonic and ethanesulphonic.

13
41. (Previously presented) A isotopically labelled arylbenzazole compound selected from the group consisting of 5-¹⁸Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole and 6-¹⁸Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole.

14
42. (Currently amended) A pharmaceutical formulation for medical use comprising a compound of claim 26 and a pharmaceutically acceptable carrier.

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43. (Currently amended) A medical preparation comprising: a therapeutically effective non-toxic amount of a compound of claim 26 and a pharmaceutically inert excipient.

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44. (Previously presented) A unit dosage of a pharmaceutical preparation as an antitumour agent in treating mammals comprising a therapeutically-effective non-toxic amount of a compound of claim 26.

17
45. (Previously presented) A method of reducing or inhibiting cancer cell growth in a mammal comprising administering to said mammal an effective amount of an pharmaceutical formulation according to claim 42.

Application No 10/069,018

Amendment dated December 19, 2003

Page 7

46. (Cancelled)

47. (Cancelled)

40
12/19/03
48. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, R^5 and R^6 represent a hydrogen atom, R^3 represents a hydrogen atom, X represents a sulfur atom, and R^2 is selected from 3'-Me, 3'-Et, 3'-Br, 3'-Cl, 3'-CN, or 3'-F.

49. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, R^5 and R^6 represent a hydrogen atom, R^3 represents a hydrogen atom, X represents an oxygen atom, and R^2 represents 3'-I.

50. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, R^5 and R^6 represent a hydrogen atom, R^3 represents 5'-Cl or 5'-Me, X represents an sulfur atom, and R^2 represents 3'-Cl.

51. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, R^5 and R^6 represent a hydrogen atom, R^3 represents 5'-Br, X represents an sulfur atom, and R^2 represents 3'-Cl.

52. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents a sulfur atom, wherein R^3 , R^5 and R^6 each represent a hydrogen atom, Q represents a direct bond, n represents 1, R^1 represents 4-F, and R^2 is selected from 3-CH₃, a hydrogen atom, 3-I, 3-Cl, or 3-Br.

53. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents a sulfur atom, wherein R^3 , R^5 and R^6 each represent a hydrogen atom, Q represents a direct bond, n represents 1, R^1 represents 6-F, and R^2 is selected from 3-CH₃, a hydrogen atom, 3-I, 3-Cl, or 3-Br.

40
12/19/03

Application No. 10/069,018

Amendment dated December 19, 2003

Page 8

- 24-54. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents a sulfur atom, wherein R^3 , R^5 and R^6 each represent a hydrogen atom, Q represents a direct bond, n represents 1, R^1 represents 5-F, and R^2 is selected from 3-CH₃, a hydrogen atom, 3-I, 3-Cl, or 3-Br.
- 25-55. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents a sulfur atom, wherein R^3 , R^5 and R^6 each represent a hydrogen atom, Q represents a direct bond, n represents 1, R^1 represents 7-F, and R^2 represents 3-CH₃.
- 26-56. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents a sulfur atom, wherein R^3 , R^5 and R^6 each represent a hydrogen atom, Q represents a direct bond, n represents 2, R^2 represents 3-CH₃, and R^1 represents a 4,5-diF, 4,6-diF, 5,7-diF, or 6,7-diF.
- 27-57. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents S, Q represents a direct bond, one of R^5 and R^6 represents a hydrogen atom and the other represents -C(O)CH(R^8)NH₂, R^3 represents a hydrogen atom, n represents 0, R^2 represents a hydrogen atom and R^8 represents a group selected from -CH₃ or -(CH₂)₄NH₂.
- 28-58. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents S, Q represents a direct bond, one of R^5 and R^6 represents a hydrogen atom and the other represents -C(O)CH(R^8)NH₂, R^3 represents a hydrogen atom, n represents 0, R^2 represents 3-CH₃ and R^8 represents a group selected from -CH₃, -(CH₂)₄NH₂, or CH₂OH.
- 29-59. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents S, Q represents a direct bond, one of R^5 and R^6 represents a hydrogen atom and the other represents -C(O)CH(R^8)NH₂, R^3 represents a hydrogen atom, n represents 0, R^2 represents 3-Cl and R^8 represents a group selected from -CH₃ or -(CH₂)₄NH₂.

Application No. 10/069,018

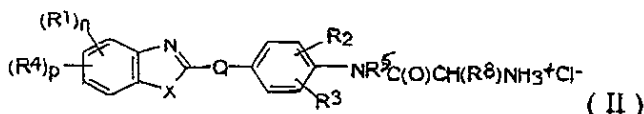
Amendment dated December 19, 2003

Page 9

30 60. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents S, Q represents a direct bond, one of R^5 and R^6 represents a hydrogen atom and the other represents $-C(O)CH(R^8)NH_2$, R^3 represents a hydrogen atom, n represents 1, R^2 represents 3- CH_3 , R^1 represents 5-F, and R^8 represents a group selected from $-CH_3$, $-(CH_2)_4NH_2$, or a hydrogen atom.

31 61. (New) An arylbenzazole compound of Claim 26 or 27 wherein $p = 0$, X represents S, Q represents a direct bond, one of R^5 and R^6 represents a hydrogen atom and the other represents $-C(O)CH(R^8)NH_2$, R^3 represents a hydrogen atom, n represents 1, R^2 represents 3- CH_3 , R^1 represents 6-F, and R^8 represents a group selected from $-CH_3$, $-(CH_2)_4NH_2$, or a hydrogen atom.

32 62. (New) An arylbenzazole compound represented by the structural formula II below, or a pharmaceutically acceptable salt thereof



wherein

X represents S or O;

R^1 independently represents fluoro, iodo or trimethyltin;

R^2 represents hydrogen, NO_2 , N_3 , halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3 ;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

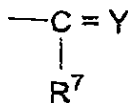
R^4 independently represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R^5 represents hydrogen, an amino acid, an alkyl, or a group

Application No. 10/069,018

Amendment dated December 19, 2003

Page 10



wherein Y represents O or S, and R⁷ represents alkyl or -CH(R⁸)NH₂ where R⁸ represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, -CH₂- or -CH=CH-;

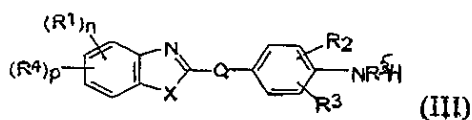
p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

subject to the following provisos:

- (a) alkyl or substituted alkyl groups include linear, branched or cyclic structures but when present as linear or branched structures in the compound or as a moiety in another group such as alkoxy they are composed of less than ten carbon atoms;
- (b) p represents zero or 1 when n represents 3;
- (c) when a group is optionally substituted, unless otherwise specified, the substituent is selected from one or more of the following: a halogen, OH, SH, NH₂, COOH and CONH₂.

33-63. A method of preparing the compound of claim 62 comprising reacting a compound of formula III below



with a BOC-protected amino acid, followed by hydrochloric acid.